Peanut allergy: An increasingly common life-threatening disorder

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Allergic reactions to peanuts in children have become a significant medical and legal concern worldwide, with a rising incidence of this potentially fatal condition. Peanut allergy represents an immunoglobulin E (IgE)—mediated hypersensitivity reaction to peanut proteins and is responsible for the majority of cases of food-induced anaphylaxis. Even trace quantities of peanut in a sensitized individual can be fatal, with rapid onset of symptoms often including the cutaneous findings of urticaria, angioedema, or a diffuse nonspecific dermatitis. Peanut allergy is usually a lifelong condition, since only about 20% of affected individuals outgrow it. Some schools ban peanut butter and jelly sandwiches, once a common dietary option, as fear of medical and legal consequences is escalating. Children with peanut allergy and their families should be knowledgeable about management strategies, including carrying and properly administering self-injectable epinephrine. New immunotherapeutic options are being investigated and appear promising. (J Am Acad Dermatol 2012;66:136-43.)

INTRODUCTION

Food allergies affect 6% to 8% of children younger than 4 years of age and 4% of the United States (US) population older than 10 years.[1-3] The most common foods inducing clinical reactions are cow's milk, wheat, egg, soy, peanut, tree nuts (walnuts, hazelnuts, almonds, cashews, pecans, and pistachios), fish and shellfish.[4] Peanut allergy is a severe immunoglobulin E (IgE)—mediated hypersensitivity reaction to proteins found in these legumes. Peanut allergy represents the majority of cases of food-induced anaphylaxis.[5-8] Exposure to even trace quantities of peanuts in a sensitized individual can lead to a fatal reaction. Its onset is generally in childhood, affecting approximately 1% of children younger than 5 years.[9-11] Peanut allergy is usually a lifelong condition, although about 20% of individuals outgrow it.[12] Clinical features develop rapidly after exposure, with cutaneous, gastrointestinal, and respiratory manifestations.[1] Peanut allergy in the pediatric population is a growing societal concern, as the outcome can be fatal and its prevalence is increasing.

Abbreviations used:

IgE:	immunoglobulin E
ImmunoCAP-FEIA:	IgE fluorometric enzyme immunoassay
ISS-oligodeoxynucleotide:	immunostimulatory sequence containing oligodeoxynucleotides
RAST:	radioallergosorbent test
SPT:	skin prick test

HISTORY

Peanuts have been cultivated in South America since 2000 to 3000 BC.[13] They were grown as far north as Mexico and were brought to Europe at the time of the Spanish empire in the Americas, quickly spreading to Africa and Asia. In the United States, peanuts were originally used as livestock feed, but were later grown commercially for oil, food, and as a cocoa substitute. The popularity of peanuts as a food increased after the American Civil War (1861-1865). In the early 20th century, George Washington Carver, an eminent American biochemist, revolutionized the peanut industry.[13] He developed over 300 new uses for the peanut in food and in manufactured products, such as plastics, linoleum, adhesives, bleaches, and shampoos. Peanuts are valued today because they are a source of easily digested protein and have extensive food and industrial applications.

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PREVALENCE

In 2002, 1.1% of the US population, approximately 3 million people, reported allergy to peanuts and tree nuts, which contrasts with 0.6% in 1997.[3] This increase was due primarily to a rise in peanut allergy prevalence among young children, from 0.4% to 0.8%.[3] Other studies have confirmed that the prevalence of peanut allergy is ascending in children. Tariq et al[14] followed up a cohort of 3- and 4-year-old children born between 1994 and 1996 and a cohort born in 1989 from the Isle of Wight, United Kingdom. Their results showed a twofold increase in reported peanut allergy (0.5%-1%) and a threefold jump in sensitization (1.1%-3.3%) between the two groups. After further analysis with oral challenges, the prevalence of peanut allergy was estimated to be 1.5% among the subjects in the 1994-1996 cohort. In a US nationwide cross-sectional, random digit dial telephone survey, adult surrogates from 4374 households were interviewed. Peanut allergy was reported for 0.4% of children and 0.7% of adults.[3] Similar statistics have been presented in other studies. The estimated prevalence of peanut allergy in developed countries is between 0.6% and 1.0%.[12]

The cause of a rising prevalence of peanut allergy is unknown. Although genetic and environmental factors likely play a role, several theories have emerged to explain this recent phenomenon. The hygiene hypothesis claims that decreased early life exposures to specific viral infections and endotoxins are leading to an increase in allergies.[15] Another theory centers on the maternal ingestion of peanuts during pregnancy and lactation as well as the timing of peanut introduction to infants or children.[1,16] In one study, a significant number of infants younger than 4 months already had a positive skin test to peanuts, likely due to exposure in utero or from breast milk.[5] Another analysis showed that most individuals with peanut allergy had been breastfed for the first several months of life.[17] Other factors may play a role, such as increased peanut consumption, use of peanut-containing non-food products, and early introduction of potentially cross-reacting proteins such as soy or carob.[18-21] Commonly used processing techniques, including roasting, emulsifying, and mixing additives with peanuts, possibly cause increased antigenicity and may be implicated in the rising incidence of allergy.[18]

CAPSULE SUMMARY

- Peanut allergy, an IgE-mediated hypersensitivity to specific peanut proteins, is increasing in prevalence among children and adults worldwide, with only about 20% of affected children outgrowing it.
- Reactions develop rapidly and include cutaneous manifestations, such as urticaria and angioedema, as well as gastrointestinal, respiratory, and other anaphylactic features.
- Diagnosis is made by clinical history and diagnostic testing.
- Management includes patient/family education and emergency treatment.
- Novel immunotherapeutic options currently being investigated hold promise for improved treatment.

PATHOPHYSIOLOGY

Sensitizing exposure to the peanut protein allergen in susceptible individuals leads to the production of protein-specific IgE, which is then bound to high-affinity IgE receptors on mast cells or basophils. Upon re-exposure to the allergen, adjacent cell-bound IgE and peanut allergen cross-link, causing degranulation of preformed inflammatory mediators such as histamine, prostaglandins, and leukotrienes. Furthermore, the cells produce interleukin (IL)-4 and IL-13, cytokines, and chemokines, which recruit other inflammatory cells. These chemical reactions lead to the clinical symptoms of allergy and anaphlyaxis.[4]

The allergenic components of peanuts are the proteins of the cotyledon.[4] Eight peanut allergens have been identified, Ara h1 to Ara h8, named after the scientific name for this legume, *Arachis hypogaea*.[22-27] Ara h1 and Ara h2 are the major peanut allergens implicated in most reactions and belong to the vicilin and conglutin families of storage proteins, respectively. More than 90% of peanut-allergic patients have IgE antibodies to these two proteins. Similarly, 45% to 95% of peanut-allergic patients have IgE antibodies to Ara h3, a related protein.[4] The distribution of sensitivity to the various peanut antigens differs among geographic locations.[28] The linear IgE-binding epitopes of the major peanut allergens have been identified by using overlapping peptides and serum peanut-specific IgE from patients with documented peanut hypersensitivity.[29] Allergenic epitopes are generally resistant to acid, heat, and enzymatic degradation. However, peanut allergens can be modified by food processing techniques. Dry roasting increases allergenicity when compared with boiling and frying peanuts.[30] Roasting leads to the Maillard reaction, a

Table I. Common foods cross-reacting with peanuts in IgE-mediated allergy

Legumes
Pea, bean, carob bean, kidney bean, garbanzo bean, clover lupine, lentil
Tree nuts
Almond, cashew, walnut, Brazil nut, chestnut, hazelnut, macadamia nut, pine nut, pistachio, pecan
Seeds
Sesame

nonenzymatic process resulting in glycosylation of amino groups to form stable advanced glycation end-products.[31] Peanuts that were roasted were found to have 22-fold higher extractable Ara h1 compared with raw peanuts.[31]

There can also be a high degree of cross-reactivity between peanuts and other plant proteins, via an IgE-mediated mechanism (Table I). The peanut is a legume and shares homologous proteins with other members of the legume family such as peas, beans, carob beans, kidney beans, garbanzo beans, clover, lupines, and lentils.[28] Studies have demonstrated that 38% to 79% of individuals with clinical reactions to a single legume show IgE binding (positive skin test/RAST) to a variety of legumes.[18] However, in a study using oral challenge, only 5% of patients with peanut allergy had a clinical positive challenge to more than one legume.[18] There is also appreciable cross-reactivity between peanuts and tree nuts, with one study showing a 2.5% co-allergy rate.[32] Although cross-reactivity is found more commonly during in vitro tests and does not usually result in serious clinical symptoms, patients with peanut allergy should be cognizant of such a risk. Peanut-allergic patients must exercise caution when ingesting possibly cross-reacting allergens. If a clinical reaction does manifest, they should be advised to avoid future exposure to that particular allergen.

CLINICAL FEATURES

When life-threatening anaphylaxis to peanuts occurs, it is generally the result of oral ingestion. Although clinical reactions may occur from cutaneous or airborne exposure to peanuts, they are rarely fatal. Clinical symptoms of peanut allergy can develop precipitously, becoming manifest within seconds and up to 2 hours following exposure to peanut protein.[1] More than 95% of reactions occur within 20 minutes.[4] Extremely low quantities of peanut proteins can induce subjective and objective symptoms and are much less than found in a typical peanut, which has 200 mg of protein.[33] Subjective symptoms may manifest with doses as low as 100 μg, whereas objective symptoms may occur at doses of 2 mg.[33] Fatal reactions rarely transpire on first ingestion.[1] Reactions can be biphasic in one third of patients, with allergic symptoms recurring 1 to 8 hours after the initial symptoms have resolved.[12] Individuals with life-threatening reactions are usually adolescents or adults with a history of asthma and atopy. A survey involving participants of a voluntary national peanut/tree nut allergy registry provided information on clinical features.[6] The average age at diagnosis was 14 months with symptoms occurring after the first known peanut ingestion in 75% of children. The onset of symptoms was usually within 3 minutes. Exposure to the allergen was most commonly through ingestion (91%), followed by presumed skin contact (8%) and inhalation (1%). Most parents described the initial reaction taking place at home (70%), whereas subsequent reactions (70%) often occurred at other locations such as schools, restaurants, and the homes of relatives or friends.

Table II. Cutaneous manifestations of peanut allergy

Urticaria
Angioedema
Pruritic erythematous rash

Clinical reactions frequently involve multiple organs including the cutaneous, cardiovascular, gastrointestinal, and respiratory systems.[34] Two systems were affected in 31% of initial reactions, and 3 systems in 21%.[17] In an oral challenge study in France, clinical symptoms due to peanut allergy included a flare of atopic dermatitis (46%), urticaria/angioedema (32%), asthma (15%), generalized anaphylaxis (5%), and gastrointestinal symptoms (3%).[35] Nearly all reactions involve the skin (89%), including a pruritic, erythematous eruption and acute urticaria with or without angioedema (Table II).[34] Isolated cutaneous manifestations may occur, but these patients usually have lower serum peanut-specific IgE levels than those with respiratory and/or gastrointestinal symptoms, with a median of 1.25 kUA/L compared with 11.65 kUA/L in one study.[36] Respiratory features were observed in 52% of patients and included upper and lower respiratory tract symptoms, laryngeal edema, repetitive coughing, voice change, and wheezing (Table III).[17] The gastrointestinal tract was involved in 34% of cases with symptoms such as acute vomiting, abdominal pain, or diarrhea (see Table III).[17] Anaphylaxis, the most severe manifestation, includes cardiovascular abnormalities such as hypotension and dysrhythmia, in addition to the previously mentioned symptoms

Table III. Extracutaneous manifestations of peanut allergy

Gastrointestinal
Vomiting
Abdominal pain
Diarrhea
Respiratory
Coughing
Laryngeal edema
Voice change
Wheezing
Anaphylaxis
Cutaneous symptoms (see Table II)
Gastrointestinal symptoms (above)
Respiratory symptoms (above)
Hypotension
Dysrhythmia

(see Table III). There is also a rare variant called food-dependent, exercise-induced anaphylaxis, whereby patients develop symptoms of anaphylaxis only if physical activity occurs within a few hours of eating a specific food, such as peanuts.[1]

DIAGNOSIS

The first step in identifying peanut as the cause of a reaction is a detailed history and physical examination (Table IV). It is important to determine the temporal association between ingestion and symptoms, the type of symptoms, the amount of peanut ingested, and whether symptoms occur after eating similar foods. A personal or family history of atopy is also noteworthy. Detection of peanut-specific IgE by either skin prick test (SPT) or in vitro assays can help with diagnosis (Table V).[4] An SPT is performed with a commercially available peanut extract, which is convenient, inexpensive, and rapidly interpretable. A wheal 3 mm larger than the negative control is considered a positive reaction.[37] An SPT for peanut allergen that yields a mean wheal size larger than 8 mm is highly likely to predict clinical reactivity.[38] SPTs have excellent negative predictive values (>95%), but poor specificity (30%-60%) and positive predictive value (<50%). Although serious reactions have rarely occurred with SPT, particularly when performed during active wheezing, no fatalities have been reported.[12] In vitro IgE tests measure allergen-specific IgE bound to standardized allergen. There are several in vitro tests available on the market. The fluoroenzyme immunoassay (ImmunoCAP-FEIA) has been used extensively in clinical studies. Results are measured semiquantitatively, ranging from less than 0.35 to greater than 100 kUA/L, with values correlating with probability of clinical reactivity but not severity of reaction.[12] Peanut-specific IgE greater than 15 kUA/L has a 95% predictive value for an allergic reaction on ingestion of peanut.[39] In vitro testing is especially useful for patients in whom antihistamines cannot be withdrawn prior to skin testing or if severe skin disease prohibits testing. Problems with this test include expense, delayed results, limited availability of approved laboratories, and lack of age-specific norms. The gold standard for confirming peanut allergy is a double-blinded, placebo-controlled peanut food challenge.[12] The patient ingests incremental portions of food or placebo, hidden in a masking vehicle or gelatin capsule at 15- to 30-minute intervals. Signs and symptoms of an allergic reaction are documented before each dose. If a reaction occurs, the challenge is stopped and treatment is provided. Although this test provides a definitive diagnosis, it is time consuming, requires close supervision by medical personnel, and is dangerous, as it carries the risk of a severe reaction.[12]

Table IV. Diagnosis of peanut allergy[1]

- Medical history indicating temporal association between eating peanuts and appearance of symptoms
- Evidence of peanut-specific IgE or positive skin prick test

MANAGEMENT

Management of peanut allergy centers on educating patients and their families on complete avoidance of peanut-containing products (Table VI). This can be difficult, as peanuts may be found in unexpected products. There is also a risk of cross-contamination by peanut products during food preparation. Careful inspection of ingredient labels and inquiry about risk of cross-contamination at restaurants is desirable. School personnel should be informed about the child's allergy and develop a plan of action to be implemented should a reaction occur. Allergic children should wear MedicAlert bracelets, notifying others of their allergy in the case of emergency.[12] There are numerous resources available for information on peanut allergy, treatments, and support.

It is essential for patients and their families to recognize the early signs of an allergic reaction upon accidental exposure. Patients should carry a self-injectable epinephrine device, such as EpiPen (Dey Pharma, LP, Basking Ridge, NJ), and they and their families should know how to properly administer the drug (Table VII).[1] Injecting epinephrine early in the course of the reaction has been shown to decrease the risk of fatal outcomes and biphasic reactions.[34] Oral antihistamines, such as diphenhydramine (1 mg/kg)

Table V. Diagnostic testing

Test	Criteria	Advantages	Disadvantages
Skin prick	Wheal 3 mm > negative control or wheal > 8 mm	Convenient	Specificity (30%-60%)
		Inexpensive	Positive predictive value (<50%)
		Rapidly interpretable	
		Negative predictive value (>95%)	
		Low risk of reaction	
In vitro peanut-specific IgE	IgE >15 kUA/L	Positive predictive value (95%)	Expensive
		No risk of reaction	Delayed results
			Limited laboratory availability
			Lack of age-specific norms
Oral food challenge	Clinical reaction	Gold standard	High risk of severe reaction
			Time-consuming

Table VI. Management of peanut allergy[1]

- Written management plan
- Patient and family education about strategies to avoid eating peanuts
- Recognition of early signs of an allergic reaction
- Treatment of early stages of allergic symptoms
- Long-term follow-up

or hydroxyzine (0.5 mg/kg), can be used as an adjunct to epinephrine. Patients with anaphylactic symptoms should be treated with intramuscular epinephrine and promptly transported to a medical facility where additional treatment can be provided, such as oxygen, inhaled albuterol, and systemic corticosteroids and antihistamines.[1] Patients are usually given a 3-day course of oral prednisone (1 mg/kg bodyweight per day) and an antihistamine.[1] Up to 30% of anaphylactic reactions have a biphasic course that can occur 1 to 8 hours after onset of symptoms, so patients should be observed under medical supervision for 4 to 8 hours after onset of allergic symptoms.[12]

FUTURE PROSPECTS

Novel treatments for peanut allergy are being investigated to provide patients with alternatives to current therapy (Table VIII). Potential immunotherapeutic options include oral peptide, mutated recombinant protein, plasmid DNA, and ISS-oligodeoxynucleotide therapy. Oral and traditional injection immunotherapy has long been avoided for peanut allergy because of a high incidence of serious side effects. Only a few protocols have been designed for the induction of oral tolerance to peanuts. A recent oral induction protocol from Spain was successful in achieving tolerance in a severely peanut-allergic child.[40] Similarly, injection immunotherapy has rarely been used to induce tolerance to peanuts. In a double-blind, placebo-controlled study of rush immunotherapy for treatment of peanut allergy, patients were given injections containing small amounts of allergen over the course of several months to develop tolerance. Patients in the treatment group were able to tolerate an increased amount of peanuts in a posttreatment food challenge.[30] However, there was a high rate of adverse reactions in response to this therapy, making it unacceptable for routine use. Blumchen et al[41] showed that a more gradual build-up protocol of oral immunotherapy administered over a longer period of time, in contrast to rush immunotherapy, appeared to be safe and effective in many patients with peanut allergy. Patients were able to tolerate a median of 1 gram of peanut protein compared with 0.19 gram prior to the immunotherapy. Mild symptoms were encountered after 2.6% of doses, while airway obstruction was seen after 1.3% of doses.[41]

In an effort to increase patient safety, peptide immunotherapy is being developed using fragments containing T-cell–reactive epitopes instead of whole peanut protein. Ara h2 peptide immunotherapy has been studied in a mouse model for peanut allergy. Pretreatment with two doses of the major peanut protein mixture prior to peanut challenge has been shown to prevent anaphylactic reactions, lower plasma histamine levels, and increase interferon gamma production by spleen cells in peanut-sensitized mice compared with controls.[15] Genetically engineered allergen proteins have also been proposed for immunotherapy, as these mutated proteins have amino acid substitutions within IgE-binding epitopes.[15] In an in vivo study, mice were sensitized with whole peanut and then desensitized by intranasal administration of mutated Ara h2, which

Table VII. Treatment of acute peanut allergy reaction[1]

1. Treatment of early stages of allergic symptoms by patient or family members
- Injection of epinephrine depending on patient's history and symptoms
- Administration of oral antihistamine (diphenhydramine, about 1 mg/kg of body weight up to 75 mg, or chlorpheniramine)

2. Transportation to emergency medical facility by emergency personnel
- Airway management and supplemental oxygen
- IM epinephrine (0.01 mL of 1:1000 dilution/kg every 10 to 20 minutes as needed; maximum 0.5 mL per dose) or IV epinephrine for severe hypotension (0.5-5 μg/min to support blood pressure)

3. Intravenous fluids and medications
- Oral, IM, or IV H1-receptor antagonist
- Oral prednisone (1-2 mg/kg body weight up to 75 mg) for 3 days or IV methylprednisolone (2 mg/kg body weight up to 250 mg)
- Nebulized albuterol (1.25-2.5 mg every 20 minutes, as needed or continually)
- Possible use of H2-receptor antagonist (adults: 4-5 mg of oral ranitidine/kg of body weight up to 300 mg; 50 mg IM or IV every 6-8 hours; children: 1.5 mg/kg body weight IM or IV up to 50 mg)

4. Discharge instructions
- Oral H1-receptor antagonist for 3 days
- Oral prednisone (1 mg/kg body weight per day up to 75 mg)
- Follow-up with appropriate specialist if not previously evaluated

IM, Intramuscular(ly); *IV*, intravenous(ly).

suppressed synthesis of Ara h2-IgE and resulted in decreased symptoms on oral peanut challenge compared with a control group.[15] Plasmid DNA-based immunotherapy and ISS-oligodeoxynucleotide-based immunotherapy are other potential treatments being investigated. The latter treatment uses synthetic immunostimulatory oligodeoxynucleotides containing unmethlyated cytosine-phosphate quinine motifs to prevent and treat peanut allergy. Preliminary studies show these treatments provide some protection, but there are no reports of reversal of established peanut allergy.[31,32]

Humanized anti-IgE monoclonal antibodies and traditional Chinese medicine are also being investigated for use in peanut allergy. Anti-IgE antibody binds to IgE and prevents it from binding to mast cells and basophils, thereby avoiding allergic manifestations. It has been used as a treatment for asthma and respiratory allergy.[41-45] In a recent study, patients had a significant increase in the threshold dose of peanut flour required to induce allergic symptoms after anti-IgE antibody treatment.[46] Traditional Chinese medicine has long been utilized for various allergies.[47] Recent studies investigated the Chinese herbal-derived formula FAHF-2 in a mouse model to determine its use in peanut allergy.[47] Results showed that control mice developed severe anaphylactic signs, decreased rectal temperatures, and increased plasma histamine levels after ingestion of peanut protein. In contrast, mice treated with FAHF-2 did not show signs of anaphylaxis.

Table VIII. Future therapeutic options

Oral immunotherapy
Peptide immunotherapy
Mutated recombinant protein
Plasmid DNA immunotherapy
ISS-oligodeoxynucleotide immunotherapy
Anti-IgE monoclonal antibody
Chinese traditional medicine

ISS, Immunostimulatory sequence.

PROGNOSIS

The majority of affected children remain allergic to peanuts for life. This conclusion is supported by the similar rates of peanut allergy affecting adults and children.[48] Some individuals outgrow their allergy. One study showed that peanut allergy had resolved in 18% of individuals participating in oral peanut challenges.[49] Skolnick et al[50] offered oral food challenges to individuals aged 4 to 20 years with a serum peanut-specific IgE level less than 21 kIU/L. Of those, 21.5% did not develop a reaction, likely indicating resolution of the allergy. Based on data from several studies, it is estimated that 20% of children who develop peanut allergy will outgrow it later in life. Peanut-specific IgE levels can be used to help guide which patients with peanut allergy should be considered for a formal oral food challenge. One study determined that 61% of children with IgE levels 5 of kU/L or less, 67% with levels of 2 kU/L or less, and 73% with undetectable peanut-specific IgE did not have a reaction upon oral food challenge.[48] Thus peanut specific IgE levels below 5 kU/L may help to predict resolution. Peanut allergy may recur after resolution. Fleischer[48] determined a recurrence rate of approximately 8% in patients who outgrew their peanut allergy. Consequently, recurrence should be suspected in individuals with resolved peanut allergy who develop classic symptoms following peanut exposure.

REFERENCES

1. Burks AW. Peanut allergy. Lancet 2008;371:1538-46.
2. Sampson HA. Food allergy—part 1: immunopathogenesis and clinical disorders. J Allergy Clin Immunol 1999;103:717-28.

3. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. J Allergy Clin Immunol 2003;112: 1203-7.
4. Pansare M, Kamat D. Peanut allergies in children—a review. Clin Pediatr 2009;48:709-14.
5. Moneret-Vautrin DA, Rance F, Kanny G. Food allergy to peanuts in France—evaluation of 142 observations. Clin Exp Allergy 2001;28:1113-9.
6. Sicherer SH, Furlong TJ, Munoz-Furlong A. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. J Allergy Clin Immunol 2001;108:128-32.
7. Sicherer SH, Furlong TJ, Desimone J, Sampson HA. The US Peanut and Tree nut Allergy Registry: characteristics of reactions in schools and daycare. J Pediatr 2001;138:560-5.
8. Sicherer SH, Furlong TJ, DeSimone J, Sampson HA. Self reported allergic reactions to peanut on commercial airliners. J Allergy Clin Immunol 1999;103:186-9.
9. Sampson HA. Update on food allergy. J Allergy Clin Immunol 2004;113:805-19.
10. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol 2006;117:S470-5.
11. Lee LA, Burks AW. Food allergies: prevalence, molecular characterization, and treatment/prevention strategies. Ann Rev Nutr 2006;26:539-65.
12. Al-Muhsen S, Clarke AE, Kagan RS. Peanut allergy: an overview. CMAJ 2003;168:1279-85.
13. Loza C, Brostoff J. Peanut allergy. Clin Exp Allergy 1995;25: 493-502.
14. Tariq SM, Stevens M, Matthew S, Ridout S, Twiselton R, Hide DW. Cohort study of peanut and tree nut sensitization by age of 4 years. BMJ 1996;313:514-7.
15. Nowak-Wegrzyn A. Immunotherapy for food allergy. Inflamm Allergy Drug Targets 2006;5:23-34.
16. Kemp AS, Ponsonby AL, Dwyer T, Cochrane JA, Pezic A, Jones G. Maternal antenatal peanut consumption and peanut and rye sensitization in the offspring at adolescence. Clin Exp Allergy 2011;41:224-31.
17. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics 1998;102(1):e6.
18. Sicherer SH. Clinical update on peanut allergy. Ann Allergy Asthma Immunol 2002;88:350-61.
19. Moneret-Vautrin DA, Hatahet R, Kanny G. Risks of milk formulas containing peanut oil contaminated with peanut allergens in infants with atopic dermatitis. Pediatr Allergy Immunol 1994;5:184-8.
20. Kull I, Hallner E, Lilja G. Peanut oil in vitamin A and D preparations: reactions to skin test and manifestation of symptoms. Pediatr Allergy Immunol 1999;10:21-6.
21. Fiocchi A, Restani P, Travaini M. Carob is not allergenic in peanut-allergic subjects. Clin Exp Allergy 1999;29:402-6.
22. Burks AW, Williams LW, Helm RM, Connaughton C, Cockrell G, O'Brien TJ. Identification of a major peanut allergen, Ara h I, in patients with atopic dermatitis and positive peanut challenges. J Allergy Clin Immunol 1991;88:172-9.
23. Burks AW, Williams LW, Connaughton C, Cockrell G, O'Brien TJ, Helm RM. Identification and characterization of a second major peanut allergen, Ara h II, with use of the sera of patients with atopic dermatitis and positive peanut challenge. J Allergy Clin Immunol 1992;90:962-9.
24. Burks AW, Cockrell G, Connaughton C, Karpas A, Helm RM. Epitope specificity of the major peanut allergen, Ara h II. J Allergy Clin Immunol 1995;95:607-11.
25. Burks AW, Cockrell G, Stanley JS, Helm RM, Bannon GA. Recombinant peanut allergen Ara h I expression and IgE binding in patients with peanut hypersensitivity. J Clin Invest 1995;96:1715-21.
26. Koppelman SJ, Knol EF, Vlooswijk RA. Peanut allergen Ara h 3: isolation from peanuts and biochemical characterization. Allergy 2003;58:1144-51.
27. Mittag D, Akkerdaas J, Ballmer-Weber BK. Ara h 8, a Bet v 1-homologous allergen from peanut, is a major allergen in patients with combined birch pollen and peanut allergy. J Allergy Clin Immunol 2004;114:1410-7.
28. Vereda A, van Hage M, Ahlstedt S, Ibañez MD, Cuesta-Herranz J, van Odijk J, et al. Peanut allergy: clinical and immunologic differences among patients from 3 different geographic regions. J Allergy Clin Immunol 2011;127:603-7. Epub 2010 Nov 18.
29. Mueller GA, Gosavi RA, Pomés A, Wünschmann S, Moon AF, London RE, et al. Ara h 2: crystal structure and IgE binding distinguish two subpopulations of peanut allergic patients by epitope diversity. Allergy 2011 Jan 21. [Epub ahead of print].
30. Scurlock AM, Burks AW. Peanut allergenicity. Ann Allergy Asthma Immunol 2004;93:S12-8.
31. Sicherer SH, Sampson HA. Peanut allergy: emerging concepts and approaches for an apparent epidemic. J Allergy Clin Immunol 2007;120:491-503.
32. Sicherer SH, Sampson HA. Peanut and tree nut allergy. Curr Opin Pediatr 2000;12:567-73.
33. Carr WW. Clinical pearls and pitfalls: peanut allergy. Allergy Asthma Proc 2005;26:145-7.
34. Al-Ahmed N, Alsowaidi S, Vadas P. Peanut allergy: an overview. Allergy Asthma Clin Immunol 2008;4:139-43.
35. Rancé F, Kanny G, Dutau G, Moneret-Vautrin D. Food hypersensitivity in children: clinical aspects and distribution of allergens. Pediatr Allergy Immunol 1999;10:33-8.
36. Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SH. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. J Pediatr 2000;137: 749-55.
37. Bock SA, Buckley J, Holst A, May CD. Proper use of skin tests with food extracts in diagnosis of hypersensitivity to food in children. Clin Allergy 1977;7:375-83.
38. Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. J Allergy Clin Immunol 2005;115:1291-6.
39. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol 1997;100:444-51.
40. Ojeda P, Ojeda I, Pineda F, Alfaya T, Ojeda JA. Induction of oral tolerance to peanut: a successful home-based protocol. J Investig Allergol Clin Immunol 2010;20:524-8.
41. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, de Oliveira LC, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol 2010;126:83-91.
42. Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 1997;155:1828-34.
43. Casale TB, Bernstein IL, Busse WW, LaForce CF, Tinkelman DG, Stoltz RR. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. J Allergy Clin Immunol 1997;100:110-21.
44. MacGlashan DW Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 1997;158:1438-45.
45. Milgrom H, Fick RB Jr, Su JQ, Reimann JD, Bush RK, Watrous ML. Treatment of allergic asthma with monoclonal anti-IgE

antibody. rhuMAb-E25 Study Group. N Engl J Med 1999;341: 1966-73.
46. Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med 2003;348:986-93.
47. Pons L, Palmer K, Burks W. Towards immunotherapy for peanut allergy. Curr Opin Allergy Clin Immunol 2005;5:558-62.
48. Fleischer DM. The natural history of peanut and tree nut allergy. Curr Allergy Asthma Rep 2007;7:175-81.
49. Hourihane JO, Roberts SA, Warner JO. Resolution of peanut allergy: case—control study. BMJ 1998;316:1271-5.
50. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA. The natural history of peanut allergy. J Allergy Clin Immunol 2001;107:367-74.